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EXAMINER	
BHAT, NARAYAN KAMESHWAR	
ART UNIT	PAPER NUMBER
1634	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/522,592	MADJAR ET AL.	
	Examiner	Art Unit	
	NARAYAN K. BHAT	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 March 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-39* is/are pending in the application.

4a) Of the above claim(s) *1-27 and 34-39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28-33* is/are rejected.

7)☒ Claim(s) *32 and 33* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *25 January 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/9/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Election/Restrictions

2. Claims 1-39 are pending in this application

3. Applicant's election of group V invention, drawn to claims 28-33 in the reply filed on March 11, 2008 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

4. Claims 1-27 and 34-39 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention of group I-IV and VI-VII there being no allowable generic or linking claim.

5. Claims 28-33 are under prosecution.

Specification

6. Applicant's remarks on October 22, 2007 (Remarks pg. 3), to identify peptide sequence (labeled as amino acids unedited mRNA) by SEQ ID NO. 38 were entered.

Claim Objections

7. Claims 32 is objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim should refer other claims in the alternatives only See MPEP § 608.01(n). For compact prosecution, claim 32 is interpreted as dependent from claim 28.

8. Claims 33 is objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim should refer other claims in the alternatives only See MPEP § 608.01(n). For compact prosecution, claim 33 is interpreted as dependent from claim 28.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claim 32 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

11. Claim 32 is indefinite because primers have been identified with three different identifiers (e.g., PCR9, actual sequence and SEQ ID 31) and therefore it is not clear which of the identifiers define the primers of the claimed invention.

Claim Interpretation

12. For examination of the claims, recitation of the phrase "an mRNA which may be edited" is interpreted broadly to encompass RNA processing. Claim recitation of the phrase "where appropriate" is interpreted broadly to encompass the step recitation as an optional step and therefore not a required step.

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

15. Claims 28-31 and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stanton et al (USPGPUB NO. US2001/0034023 published Oct. 25, 2001) in view of Larsen et al (Human mutation, 1999, 13, 318-327).

Regarding claim 28, Stanton et al teaches a SSCP method for obtaining, under given analytical conditions, the editing profile of an mRNA which may be edited, using a specific tissue sample or using a sample of a population of eukaryotic cells, said method comprises extracting the total RNAs of from eukaryotic cell lines and tissue samples and purifying the RNA by acid- phenol protocol (paragraphs 0973-0974, step 'a' of the claim).

Stanton et al also teaches the reverse transcription of the RNAs to generate cDNA (paragraph 0974) and further teaches amplifying the cDNA by PCR (paragraph 0975), which generates the double-stranded DNA (step 'b' of the claim). Stanton et al also teaches the PCR amplification of the DNAs using a pair of primers specific for a particular gene and said primers being labeled with a fluorescent dye, i.e., fluorophore (paragraphs 0085-0088). However it is noted in the SSCP method, Stanton teaches an alternative way to label the PCR product using radioactive isotope (paragraph 0975).

Stanton et al also teaches that the PCR products are produced from the 5' end of the gene (paragraph 0975), thus able to capture all transcripts originating from 5' end of the gene, which may be processed differently at 3' end. The teachings of Stanton et al thus encompass mRNA, which may be edited and primers are chosen so as to amplify all the editing forms potentially present in the RNA extract (step 'c' of the claim).

Stanton et al are silent about purification and quantifying the PCR product. However, both steps 'c' and 'd' are "where appropriate steps", which are interpreted broadly as optional steps to carry out SSCP.

Stanton et al also teaches denaturation (i.e., dissociation) of the double stranded DNAs to single stranded DNAs by heating followed by abrupt cooling (paragraph 0977, step 'f' of the claim) and separation of single stranded DNAs by gel electrophoresis (paragraph 0978, step 'g' of the claim). Stanton et al also teaches obtaining the electrophoretic profile by reading the mobility difference and acquiring data (paragraph 0977-0978). The electrophoretic profile taught by Stanton et al is the editing profile of the claim as defined in the instant specification (See instant specification, USPGPUB, paragraph 0123).

Stanton et al teaches acquisition of the editing profile data in DNA sequencing to catalog sequence variation using the software associated with the fluorescence reader (paragraph 0415). However, Stanton et al are silent about capillary electrophoresis and acquiring fluorescence data associated with fluorescent reader system in the SSCP method.

Regarding claim 29, Stanton et al teaches that the pair of primers used in step c) is chosen such that the PCR products obtained are 200 bp thus meeting the limitation of at least 100 bases in length as claimed (paragraph 0976).

Regarding claims 30 and 31, Stanton et al teaches that mRNA which may be edited is that of Serotonin 5-HT 2Creceptor (Table 3, pg. 114, last 5 lines, paragraph 0114), which is a membrane receptor as defined by instant claim 31.

Regarding claim 33, Stanton et al teaches a SSCP method for obtaining, under given analytical conditions, the editing profile and the editing rate of an mRNA which may be edited, using a specific tissue sample or using a sample of a population of

eukaryotic cells, characterized in that it comprises the following steps: a) obtaining the electrophoretic profile, i.e., editing profile by means of the SSCP method (Example 13, paragraphs 0970-0978, step 'a' of the claim). Stanton et al also teaches comparing the sequence variation profile obtained by SSCP method with known variants, i.e., standard profile in the gene corresponding to sequence variation profile for known mRNAs following a drug treatment (paragraph 0114, Example 16, paragraphs 1007-1022, step 'b' of the claim). Stanton also teaches the sequence variations of a known gene before and after drug treatment (Example 16, paragraphs 1007-1011), thus teaching a ratio of sequence variation ratio of known to new, which is the editing rate as defined in the instant specification (Instant specification, USPGPUB, paragraph 0145). Teachings of Stanton et al thus encompass selecting known editing profile and associating with editing rate (steps 'c' and 'd' of the claim).

Regarding claim 28, Stanton et al are silent about capillary electrophoresis and acquiring fluorescence data associated with fluorescent reader system in the SSCP method.

However, fluoresce monitoring and capillary electrophoresis were known in the art before the claimed invention was made as taught by Larsen et al, who teaches a high-throughput SSCP analysis by automated capillary electrophoresis and further teaches generating PCR amplified double stranded DNA using fluorescently labeled primer (pg. 319, column 2, See PCR amplification section). Larsen et al also teaches separation of single stranded DNAs by capillary electrophoresis (pg. 320, column 1, paragraph 2) and obtaining the electrophoretic profile by reading the fluorescence and

acquisition by means of the of the genetic analyzer detection system associated with fluorescence reader (pg. 319, column 1, paragraph 1, pg. 320, column 1, paragraph 2).

Larsen et al also teaches that fluorescent labeling, automated capillary electrophoresis decreases the workload and increases the throughput dramatically compared with analysis by gel electrophoresis (pg. 319, column 1, paragraph 3).

It would be have been prima facie obvious to one having the ordinary skill in the art at the time the invention was made to modify the SSCP method of Stanton et al with fluorescent labeling and automated capillary electrophoresis method of Larsen et al.

One having the ordinary skill in the art would have been motivated to modify the SSCP method of Stanton et al with a reasonable expectation of success with the expected benefit of using fluorescent labeling, automated capillary electrophoresis decreasing the workload and increasing the throughput dramatically as compared with analysis by gel electrophoresis as taught by Larsen et al (pg. 319, column 1, paragraph 3), thus avoiding hazardous radioactive isotopes and increasing the throughput of the SSCP detection method of Stanton et al.

16. Claims 28 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Maekawa et al (Biochem. biophys. res. comm. 1996, 223, 520-525, cited in IDS filed May 9, 2005) in view of Larsen et al (Human mutation, 1999, 13, 318-327).

Regarding claim 28, Maekawa et al teaches a SSCP method for obtaining, under given analytical conditions, the editing profile of an mRNA which may be edited, using a specific tissue sample or using a sample of a population of eukaryotic cells, said method

comprises extracting the total RNAs of from eukaryotic cell lines and tissue samples and purifying the RNA by guanidinium isothiocyanate/ and phenol chloroform extraction (pg. 521, paragraph 3, See the RNA preparation and cDNA synthesis section, See Table 1 and 2 for list of samples, step 'a' of the claim).

Maekawa et al also teaches the reverse transcription of the RNAs to generate cDNAs (pg. 521, paragraph 3, See the RNA preparation and cDNA synthesis section) and further teaches amplifying the cDNA by PCR (pg. 521, paragraph 5, See the Procedures for PCR section), which generates the double-stranded DNA (step 'b' of the claim). Maekawa et al also teaches the PCR amplification of the DNAs using a pair of primers specific for LDH A or B cDNA and said primers being labeled with a fluorescent dye, i.e., fluorophore (pg. 521, paragraphs 4 and 5, See design and synthesis of fluorescence labeled primers and procedures for PCR section).

Maekawa et al also teaches that primers are located at the beginning of exon 2 region, i.e., near 5' end of the mRNA (Fig. 1, See the legend) and further teaches that two forms of LDH mRNA are detected by the primer (pg. 521, See the design of the primer section). Maekawa also teaches that expression of LDH A and B is tissue specific and developmentally regulated, thus teaching they are expressed differentially (pg. 520, paragraph 2). The teachings of Maekawa et al thus encompass mRNA, which may be edited and primers are chosen so as to amplify all the editing forms potentially present in the RNA extract (step 'c' of the claim).

Maekawa et al further teaches quantifying the PCR product (pg. 521, paragraph 5, and See procedure for PCR section) and further teaches filling in the amplified

product to generate blunt end (pg. 521, paragraph 5, and See procedure for PCR section). Teachings of Maekawa et al of quantifying the PCR product and generating blunt end products encompass both steps 'd' and 'e' of the claim.

Maekawa et al also teaches denaturation of the double stranded DNAs at 80C (dissociation of the double stranded DNA by heating) and separation of DNA by gel electrophoresis (pgs. 521 and 522, See SSCP analysis section). Maekawa et al also teaches obtaining the electrophoretic profile, i.e., editing profile as defined in the instant specification (See instant specification, USPGPUB, paragraph 0123). Maekawa et al further teaches reading of the fluorescence and, where appropriate, acquisition of the profile data by means of fragment manager software associated with the fluorescence reader as claimed (Fig. 2A and B, See the figure legend, pgs. 521 and 522, See SSCP analysis section)

Regarding claim 29, Maekawa et al teaches that the pair of primers used in step c) is chosen such that the PCR products obtained are 184 bp thus meeting the limitation of at least 100 bases in length (pg. 521, paragraph 4, See design and synthesis of fluorescence-labeled primers section).

Maekawa et al are silent about abrupt cooling step and capillary electrophoresis.

However, abrupt cooling and capillary electrophoresis were known in the art before the claimed invention was made as taught by Larsen et al, who teaches a high-throughput SSCP analysis by automated capillary electrophoresis and further teaches dissociating double stranded DNAs in to single stranded DNA by heating and abrupt cooling (pg. 320, column 1, See PCR amplification section). Larsen et al also teaches

separation of single stranded DNAs by capillary electrophoresis (pg. 320, column1, paragraph 2) and obtaining the electrophoretic profile by reading the fluorescence and acquisition by means of the of the genetic analyzer detection system associated with fluorescence reader (pg. 319, column 1, paragraph 1, pg. 320, column 1, paragraph 2).

Larsen et al also teaches that the automated capillary electrophoresis decreases the workload and increases the throughput dramatically compared with analysis by gel electrophoresis (pg. 319, column 1, and paragraph 3).

It would be have been prima facie obvious to one having the ordinary skill in the art at the time the invention was made to modify the SSCP method of Maekawa et al with abrupt cooling and automated capillary electrophoresis method of Larsen et al.

One having the ordinary skill in the art would have been motivated to modify the SSCP method of Maekawa et al with a reasonable expectation of success with the expected benefit of using an automated capillary electrophoresis for decreasing the workload and increasing the throughput dramatically as compared with analysis by gel electrophoresis as taught by Larsen et al (pg. 319, column 1, paragraph 3), thus saving time and increasing the throughput of the SSCP detection method of Stanton et al.

17. Claims 28 and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stanton et al (USPGPUB NO. US2001/0034023 published Oct. 25, 2001) in view of Larsen et al (Human mutation, 1999, 13, 318-327) and further in view of Gelfand et al (USPN 5,487,902 issued Jul. 30, 1996).

Claim 32 is interpreted as dependent from claim 28. Teachings of Stanton et al and Larsen et al regarding claim 28 are described in this office action in pages 5 and 6.

Regarding claim 32, Stanton et al teaches a SSCP method to characterize sequence variation in genes comprising 5-HT2C receptor (Example 13, paragraphs 0114, 0970-0978, Table 3, pg. 114, last 5 lines) and further teaches primers are labeled with fluorophores (paragraphs 0085-0088). Stanton et al and Larsen et al are silent about primers of SEQ ID NO. 36 and 37. However, primers for PCR was known in the art before the time of the claimed invention was made as taught by Gelfand et al, who teaches a process of detecting a target nucleic acid using primers in a PCR amplification assay (column 2, lines 52-67). Gelfand et al. also provides guidance in the choosing of primers: "The primer must be sufficiently long to prime the synthesis of extension products in the presences of the agent for polymerization. The exact length and composition of the primer will depend on many factors, including temperature of the annealing reaction, source and composition of the primer, proximity of the probe annealing site to the primer annealing site, and ratio of primer: probe concentration. For example, depending on the complexity of the target sequence, the oligonucleotide primer typically contains about 15-30 nucleotides, although a primer may contain more or fewer nucleotides. The primers must be sufficiently complementary to anneal to their respective strands selectively and form stable duplexes to replicate chain of defined length" (column 8 lines 3-34).

It would be have been prima facie obvious to one having the ordinary skill in the art at the time the invention was made to modify the SSCP method of Stanton et al and Larsen et al with primer design technique of the method of Gelfand et al.
One having the ordinary skill in the art would have been motivated to select any number of primers including SEQ ID Nos. 36-37 for use in detecting the 5-HT-2C receptor region of defined length during amplification or extension as taught by Gelfand et al (column 7, lines 27-67 and column 8, lines 1-34).

Conclusion

18. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Narayan K. Bhat whose telephone number is (571)-272-5540. The examiner can normally be reached on 8.30 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram R. Shukla can be reached on (571)-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Narayan K. Bhat/

Examiner, Art Unit 1634

Narayan K. Bhat, Ph. D.

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